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The Commissioner of Patents

7 October 1999

Sir

IN THE MATTER OF International Patent Application No. PCT/AU98/00490 in the name of THE UNIVERSITY OF QUEENSLAND
Our Ref: VS:F:FP9849

We refer to the Second Written Opinion dated 14 September 1999 issued by the International Preliminary Examining Authority in respect of this application.

Substitute pages 14, 55, 60, 62 and 63 are lodged herewith, together with a working copy indicating the nature and location of the proposed amendments.

Favourable reconsideration is requested.

Yours respectfully

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The Commissioner of Patents

24 August 1999

Sir

IN THE MATTER OF International Patent Application No. PCT/AU98/00490 in the name of THE UNIVERSITY OF QUEENSLAND
Our Ref: VS:PN:FP9849

We refer to the first written opinion dated 9 March 1999 issued in respect of this application, and offer the following comments in response to the objections of the Examiner, Marie-Anne Fam. Extension of time up to 9 September 1999 has been allowed within which to lodge a response.

The invention relates to compounds which have the ability to act as antagonists to G protein-coupled receptors, and in particular to C5a receptors. The three-dimensional structure of the C5a receptor protein is not known, and it is possible that such a structure may not be elucidated within the next 10 years. Because of the functional importance of the C5a receptor, as described in the introductory portion of the specification, intensive effort has been directed to identifying antagonists of this and other G protein-coupled receptor proteins. However, despite this effort, only a relatively small number of antagonists has been identified, and of these all have an unconstrained, essentially linear structure, as disclosed in some of the references cited by the Examiner. We particularly emphasise that no previously-known agonist or antagonist is a cyclic peptide.

The three dimensional framework structure defined in claim 1 was devised on the basis of the three-dimensional structures for active cyclic and constrained acyclic compounds which are described in the present specification. It is clear in the context of the specification when read as a whole that the role of this structure is to position the amino acid side chains which are attached to the framework in the correct three-dimensional space to enable them to interact most effectively with the C5a receptor. Thus the structure acts as a scaffold of the dimensions defined by structure I in claim 1. These dimensions are derived from the NMR solution structures obtained by the inventors; see Example 2. In addition to cyclic peptides, the invention provides acyclic compounds which have a constrained three-dimensional structure such that the side claims A, B, C and D fit the three-dimensional space defined in Structure I. The skilled addressee of the specification will be well aware that such a constraint can be provided via non-covalent interactions

such as hydrogen bonding, hydrophobic interactions, or steric hindrance. This is illustrated in Example 2 at page 34 lines 13 to 28.
Persons skilled in the art of drug design would be able to identify the three-dimensional structures of any of their own compounds using well-known, routine structure determination techniques, such as two-dimensional NMR spectroscopy for solution structure determination as illustrated in example 2, or X-ray crystallography for solid structure determination. Furthermore, even a chemist at undergraduate level would be aware that C-C, C-N and C-O bonds are 1.3 to 1.5 Å in length. Clearly on a fair reading of the specification as a whole any structure possessing the *combination* of substitutions defined by A, B, C and D in the three dimensional conformation defined in claim 1 would be expected to have agonist or antagonist activity.

Such a skilled person would have no difficulty in establishing whether a given protein, peptide or non-peptide compound was capable of adopting the confirmation required to form the framework defined by co-ordinates A, B, C, and D in claim 1. It is therefore respectfully submitted that, given the pioneering disclosure of the inventors, there is ample justification in the specification to claim not only the specific cyclic and constrained acyclic peptides and derivatives described in the specification, but the general three-dimensional scaffold as defined in claim 1. The disclosure would enable a person skilled in the art to devise other cyclic or acyclic constrained structures within the scope of claim 1. It is therefore requested that objection 1 of Box VIII should be withdrawn.

With reference to the documents cited in Box V, it is respectfully pointed out that all of the cited references disclose either unconstrained *linear* peptide agonists or low molecular weight *protein* antagonists of C5a receptor, and are therefore clearly distinct from the cyclic or constrained acyclic low molecular weight G protein-coupled receptor antagonists of the invention. The skilled addressee of the specification would readily recognise that the claimed compounds are structurally distinct from the compounds disclosed in the citations, and cannot be predicted from the disclosures of these citations.

The peptides described in the citations are not very active either as agonists or as antagonists, and their three-dimensional structures for the most part have not been identified. The only publications describing any structure are those of which the present inventors are co-authors (D2, D3, D7, and D8). None of the citations teaches anything about the probable three-dimensional structural framework of highly active antagonists or agonists, or about the probable specific composition of such highly or active compounds. In contrast, the present application for the first time reports the precise three-dimensional structural requirements for binding to a C5a receptor, and specifically for highly potent agonists and antagonists. The specification also discloses specific novel cyclic compounds and constrained acyclic compounds.

The only citation which mentions anything about a "cycle" discloses only a cyclic residue in a linear peptide, in contrast to the macrocyclic structures required in the present application. Indeed, this reference teaches away from the present invention, since the presence of the cyclic moiety resulted in loss of activity of the linear agonist peptides examined in this reference.

The inventors' detailed comments on the citations are attached. Copies of the papers by Ember et al and by Kawai et al referred to therein in relation to D2 and D4 are also attached for the Examiner's convenient reference. It is also noted that these two publications are referred to in the specification at page 9 lines 24 and 25.

The Examiner comments in the continuation of Box V that "although the above citations do not specifically disclose the dimensions defined by co-ordinates A, B, C and D of the present claims, presumably this framework is an inherent feature of the peptides described in D1-D12, since these compounds function as C5a agonists or antagonists". It is submitted that this represents an extraordinary application of hindsight in the knowledge of the invention, and is therefore impermissible. In the absence of a *specific* disclosure of each and every one of the features of the claimed invention the invention is novel, and unless there is a *specific* suggestion of a feature and disclosure of all the other features, the invention involves an inventive step. The mere possession of a modicum of agonist or antagonist activity shows only that a compound is able to bind to the C5a receptor to some extent; in fact, not only do none of the citations disclose cyclic or constrained peptides, the conventional wisdom in the art at the priority date was that cyclisation destroys activity. If any such peptide were disclosed in any of the citations, in the context of the references as whole the skilled addressee would have been led to believe that these peptides were not useful for the purposes of the invention.

With reference to objection 2 in Box VIII, appropriate amendment is proposed. The opportunity is also taken to rectify clerical errors which have come to notice. Substitute pages 9, 11, 13 to 16, 18, 40 to 43 and 54 to 63 are lodged herewith, together with working copies indicating the nature and location of the proposed amendments. It is pointed out that basis for the term "constrained acyclic" is found at page 34 line 15, page 35 line 10 and page 43 line 17.

Favourable reconsideration is respectfully requested.

Yours respectfully

Comments by the Inventor, Dr David Fairlie, on References cited by the Examiner

Documents D1-D14 either deal with linear peptide agonists or high molecular weight protein antagonists, and are therefore not relevant to the small molecule cyclic antagonist and agonist compounds of our invention.

Furthermore, the peptides described in the citations are not very active either as agonists or antagonists, and their three-dimensional structures have not been identified (except in our own papers). They do not teach us anything about the likely three-dimensional structures of highly active agonists or antagonists, or about the likely chemical nature of highly active compounds. In contrast, our application reports for the first time the precise three-dimensional structural structures needed for highly potent agonists and antagonists, and reports the development of specific novel conformationally-constrained cyclic agonists and antagonists.

Only one paper, D7, mentions anything about a "cycle". However, this is a different type of cycle, namely a small component of a *linear* peptide rather than a large macrocycle like those shown in this application, and in fact this reference teaches away from the invention, since this "cycle" destroyed activity in the linear agonist peptides examined.

Comments on the individual citations are set out below:

D1. Journal of Immunology, Temporo et al., 158: 1377-1382, 1998.
This is one of our own papers referring to *linear* agonist peptides, and was published after our priority date of 25 June 1997. It is not relevant to our application which, in contrast, describes the development of conformationally-constrained *cyclic* agonists and antagonists.

D2. J. Immunology, Baranyi et al., 157: 4591-4601, 1996.
Most of the peptides described in this paper are derived from the C5a *receptor*, not from C5a itself, and these peptides are therefore not relevant to our application. Two peptides derived from C5a are claimed to be weak antagonists. One is derived from a region not related to the carboxy terminal region of C5a, which is the focus of our application. The other peptide, PL61 (C5a 61-74), is claimed to be a weak C5a antagonist in a cellular assay. This is contrary to results obtained in our own earlier work (Ember et al., J. Immunol. 148: 3165-3173, 1992, Tables II,III, IV; pp 3069-3070) as well as by others (eg Kawai et al., J. Med. Chem. 34: 2068-2071, 1991), which showed that the natural sequences of the carboxy terminal region of C5a are invariably full agonists, albeit with much reduced potency compared to C5a.

D3. J. Pharmacology & Exper. Therapeutics, Kawatsu et al., 278: 432-440, 1996.
This is one of our own papers, and refers to *linear* agonist peptides only. In contrast our application involves the development of conformationally-constrained cyclical agonists and antagonists.

D4. Immunology, Kaneko et al., 86: 148-154, 1995.
Again this paper refers to linear peptides only. The authors claim that a 14 amino acid segment corresponding to the C-terminal region of C5a, namely C5a 61-74, is a weak antagonist. This is essentially the same assertion as that made in D2, Baranyi et al., 157: 4591-4601, 1996, from the same laboratory, and utilizes the same assay. No other group is claiming antagonistic activity for this compound, or for any other natural sequence derived from the carboxy terminal region of C5a. We have shown that this result is incorrect (Ember et al 1992, and unpublished work).

D5. Journal of Medicinal Chemistry, Kawai et al., 34:2068-2071, 1991. This paper refers to linear peptides only as agonists. No agonist or antagonist activity is reported.

D6. Journal of Immunology, Konteatis et al., 153: 4200-4205, 1994.
This paper refers to linear antagonist peptides only. This is the only reported full antagonist reported prior to our application, and it is not very potent. It was referred to in our patent application at page 9 line 33 to page 11 line 17. Our compounds are clearly different from those of this citation.

D7. Journal of Medicinal Chemistry, Sanderson et al., 38: 3669-3675, 1995. This is one of the inventors' own papers, and refers to *linear* agonist peptides. One compound reported involves a small cyclic moiety within the linear peptide sequence; this is quite different to the much larger cyclic peptides in the present patent application. In any case the presence of the cyclic residue resulted in loss of activity. Thus this reference teaches away from cycles as useful components of agonists.

D8. Journal of Medicinal Chemistry, Finch et al., 40: 877-884, 1996.
This publication refers only to linear agonist peptides.

D9. Journal of Medicinal Chemistry, Kawai et al., 35: 220-223, 1992.
This paper refers to linear agonist peptides only.

D10. Biochemical Pharmacology, Drapeau et al., 45: 1289-1299, 1993.
This paper, which is essentially the same as D6, refers to linear peptides only. One compound was a partial agonist only, with activity depending upon the assay used.

D11. Journal of Biological Chemistry, De Martino et al., 270: 15966-15969, 1995.
This paper refers to linear agonist peptides. This is a mechanistic paper, which suggested that antagonists have to have a negative charge at the C-terminus - a proposal which we did not believe, and in fact have now shown to be incorrect, since the cyclic compounds in this application do not have a negative charge at the site which was formerly the C-terminus.

D12. Protein Science, Zhang et al., 6: 65-72, 1997.
This paper describes the structure and antagonistic activity of a protein analogue of C5a. It is not a small molecular weight molecule derived from the carboxy terminus of C5a, as described for our novel cyclic compound. It is

actually C5a with a few residues changed. There is no resemblance between this and the compounds in this application.

D13. Journal of Peptide Research Vogen et al., 51: 226-234, 1998.
This paper refers to the structure of a *linear* agonist peptide and was published after our priority date of 25 June 1997. Conformationally-constrained cyclic agonists and antagonists are not reported in this paper. Although in the last two sentences of the conclusions the authors do speculate that cyclic agonists and antagonists might be possible, no dimensions or specific structures are suggested. Thus there is nothing to lead a person of ordinary skill in the art to consider the claimed structures.

D14. Journal of Immunology, Pellas et al., 160: 5616-5621, 1998.
This paper describes the antagonistic activities of some protein analogues of C5a as for D12, this reference is irrelevant to our application.

TENT COOPERATION TREAT

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GRIFFITH HACK
GPO Box 1285K
MELBOURNE VIC 3001

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year* 19 OCT 1999

Applicant's or agent's file reference
VS:F:FP9849

IMPORTANT NOTIFICATION

International application No.	International filing date	Priority date
PCT/AU 98/00490	25 June 1998	25 June 1997

Applicant
1. THE UNIVERSITY OF QUEENSLAND et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	Marie-Anne Fam MARIE-ANNE FAM Telephone No. (02) 6283 2259

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GRIFFITH HACK
509 St. Kilda Road
Melbourne, VIC 3004
AUSTRALIE

Date of mailing (day/month/year) 24 July 1998 (24.07.98)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
International application No. PCT/AU98/00490	International filing date (day/month/year) 25 June 1998 (25.06.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 25 June 1997 (25.06.97)
Applicant THE UNIVERSITY OF QUEENSLAND et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
25 June 1997 (25.06.97)	PO 7550	AU	21 July 1998 (21.07.98)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Kari Huynh-Khuong

Telephone No. (41-22) 338.83.38

PA. .T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 26 January 1999 (26.01.99)	
International application No. PCT/AU98/00490	**Applicant's or agent's file reference**
International filing date (day/month/year) 25 June 1998 (25.06.98)	**Priority date** (day/month/year) 25 June 1997 (25.06.97)
Applicant FAIRLIE, David et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 January 1999 (04.01.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Marie-José Devillard
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
GRIFFITH HACK
GPO Box 1285K
MELBOURNE VIC 3001

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	14 SEP 1999
Applicant's or agent's file reference VS:PN:FP9849	**REPLY DUE** within **ONE MONTH** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU 98/00490	25 June 1998	25 June 1997

International Patent Classification (IPC) or both national classification and IPC

Int. Cl.[6] C07K 7/06, 7/64; A61K 38/08

Applicant

THE UNIVERSITY OF QUEENSLAND et al.

1. This written opinion is the **second** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[X]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **25 October 1999**

Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	Marie-Anne Fam MARIE-ANNE FAM Telephone No. (02) 6283 2259

WRITT PINION

ternational application No.
PCT/AU 98/00490

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-8, 10, 12, 17, 19-39, 44-53,** as originally filed,
pages , filed with the demand,
pages **9, 11, 13-16, 18, 40-43,** filed with the letter of **24 August 1999 .**

☒ the claims, pages , as originally filed,
pages , as amended under Article 19,
pages , filed with the demand,
pages **54-63 ,** filed with the letter of **24 August 1999.**

☒ the drawings, pages **1/12-12/12,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos.: **1-9 (in part), 15-16 (in part), 18 (in part) and 20-32 (in part) .**

because:

☐ the said international application, or the said claim Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

The international search was restricted to those compounds described in the examples and defined by claims 10 and 17. Consequently the opinion on claims 1-9, 15-16, 18 and 20-32 is based only on the subject matter in so far as covered by the search.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1-32 (in part)**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-32 (in part)**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-32**	**YES**
	Claims	**NO**

2. Citations and explanations

The following documents were identified in the international search report:

D1 Journal of Immunology, Volume 158, 1997, pages 1377-1382.
D2 Journal of Immunology, Volume 157, 1996, pages 4591-4601.
D3 Journal of Pharmacology and Experimental Therapeutics, Volume 278, 1996, pages 432-440.
D4 Immunology, Volume 86, 1995, pages 149-154.
D5 Journal of Medicinal Chemistry, Volume 34, 1991, pages 2068-2071.
D6 Journal of Immunology, Volume 153, 1994, pages 4200-4205.
D7 Journal of Medicinal Chemistry, Volume 38, 1995, pages 3669-3675.
D8 Journal of Medicinal Chemistry, Volume 40, 1997, pages 877-884.
D9 Journal of Medicinal Chemistry, Volume 35, 1992, pages 220-223.
D10 Biochemical Pharmacology, Volume 45, 1993, pages 1289-1299.
D11 Journal of Biological Chemistry, Volume 270, 1995, pages 15966-15969.
D12 Protein Science, Volume 6, 1997, pages 65-72.

None of D1-D12 disclose C5a antagonists or agonists with the dimensions defined by coordinates A, B, C and D. Consequently claims 1-32 (in part) are novel and inventive over the prior art.

Additional observation:

Claims 21-30 and 32 are directed to methods of treatment of the human or animal body. Under Rule 67.1 of the PCT such subject is excluded from international preliminary examination. However, claims 21-30 and 32 have nevertheless been considered since their subject matter does not contravene Australian law.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claim 1 lacks clarity with respect to the structure of amino acid D, since the nitrogen atom bearing the R^1 substituent is divalent rather than trivalent (see page 55).

A similar objection applies to claim 15 (see page 60).

2. Claim 25 is not clear in its appendency to claim 19, since claim 19 defines a compound and not a use.

3. Claim 32, which is appended to claim 20, lacks clarity. The claim refers to the method of claim 20, however claim 20 is directed to a composition.

4. Claims 1 and 15 are not fully supported by the description. The claims are exceedingly broad in scope and encompass a vast range of possible structures, however the description provides only a limited number of examples. In particular the majority of exemplified compounds are cyclic peptides of formulae II or IV; the linear derivatives described are either known from the prior art (see page 9, lines 22-37, compounds 1-7) or display reduced biological activity (see page 38, lines 9-14, compounds 8-10).

Furthermore the inventor's submissions refer repeatedly to the fact that the present invention relates to the development of cyclic agonists and antagonists, in contrast to the linear peptides of the prior art. However the claims, as presently drafted, are not limited to cyclic structures. Although claim 1 refers to a 'constrained acyclic structure', the only compound meeting this criterion and discussed in any detail appears to be the known peptide 7 (page 34, lines 13-28).

ENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

DIARIED PCT
ID. 118314

To:

Griffith Hack
GPO Box 1285K
MELBOURNE VIC 3001

WRITTEN OPINION

(PCT Rule 66)

	Date of mailing *(day/month/year)* 09 MAR 1999
Applicant's or agent's file reference VS:C:FP9849	REPLY DUE within **TWO MONTHS** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU 98/00490	25 June 1998	25 June 1997

International Patent Classification (IPC) or both national classification and IPC

Int. Cl.[6] C07K 7/06, 7/64; A61K 38/08.

Applicant

THE UNIVERSITY OF QUEENSLAND ET AL.

1. This written opinion is the **first** drawn by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:.

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[X]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **25 October 1999**

Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No. (02) 6285 3929	Authorized Officer Marie-Anne Fam MARIE-ANNE FAM Telephone No. (02) 6283 2259

WRITTEN OPINION

International application No.
PCT/AU 98/00490

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

- [X] the international application as originally filed.
- [ ] the description, pages , as originally filed,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the claims, pages , as originally filed,
  pages , as amended under Article 19,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , filed with the letter of .
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:
   - [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
   - [ ] the language of publication of the international application (under Rule 48.3(b)).
   - [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:
   - [ ] contained in the international application in printed form.
   - [ ] filed together with the international application in computer readable form.
   - [ ] furnished subsequently to this Authority in written form.
   - [ ] furnished subsequently to this Authority in computer readable form.
   - [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig

5. [ ] This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos.: **1-7 (in part), 13-14 (in part), 16 (in part) and 18-30 (in part) .**

because:

☐ the said international application, or the said claim Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

The international search was restricted to those compounds described in the examples and defined by claims 8 and 15. Consequently the opinion on claims 1-7, 13-14, 16 and 18-30 is based only on the subject matter in so far as covered by the search.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6, 8-12, 15, 17 (in part)	YES
	Claims	1-5, 7, 13, 14, 16, 18-30	NO
Inventive step (IS)	Claims	6, 8-12, 15, 17 (in part)	YES
	Claims	1-5, 7, 13, 14, 16, 18-30	NO
Industrial applicability (IA)	Claims	1-30	YES
	Claims		NO

2. Citations and explanations

The following documents, which were identified in the international search report, are relevant for novelty and inventive step considerations:

D1 Journal of Immunology, Volume 158, 1997, pages 1377-1382.

D2 Journal of Immunology, Volume 157, 1996, pages 4591-4601.

D3 Journal of Pharmacology and Experimental Therapeutics, Volume 278, 1996, pages 432-440.

D4 Immunology, Volume 86, 1995, pages 149-154.

D5 Journal of Medicinal Chemistry, Volume 34, 1991, pages 2068-2071.

D6 Journal of Immunology, Volume 153, 1994, pages 4200-4205.

D7 Journal of Medicinal Chemistry, Volume 38, 1995, pages 3669-3675.

D8 Journal of Medicinal Chemistry, Volume 40, 1997, pages 877-884.

D9 Journal of Medicinal Chemistry, Volume 35, 1992, pages 220-223.

D10 Biochemical Pharmacology, Volume 45, 1993, pages 1289-1299.

D11 Journal of Biological Chemistry, Volume 270, 1995, pages 15966-15969.

D12 Protein Science, Volume 6, 1997, pages 65-72.

Continued in supplemental box

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claims 1 and 13 are not fully supported by the description. The claims are exceedingly broad in scope and encompass a vast range of possible structures, however the description provides only a limited number of examples. In particular, the majority of antagonists/agonists exemplified are cyclic penta or hexapeptides.

   Furthermore there is insufficient information available to enable the person skilled in the art to perform the invention. The skilled addressee would have difficulty in establishing whether a given protein or peptide was capable of adopting the conformation required to form the framework defined by coordinates A, B, C and D.

2. Claim 3 lacks clarity for the following reasons:

   (i) Variable R has 2 different definitions (see page 57, lines 5 and 12).

   (ii) The definition of variable X as hydrogen appears to be chemically incorrect - see page 56, last structure wherein X is bound to the adjacent carbon atom via a double bond.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V

Claims 1-5, 7, 13, 14, 16 and 18-30 are not novel or inventive in light of D1-D10 and D12 which all disclose C5a antagonists and/or agonists; see in particular

D1 page 1379, Table 1 and page 1351, Table II.

D2 page 4592, column 1, 'Peptide Synthesis'.

D3 page 434, Table 1.

D4 page 150, figure 1 and page 153, Table 1.

D5 page 2070, Table II, compounds 14 and 15.

D6 page 4201, Table 1

D7 page 3670, Table 1.

D8 page 878, Tables 1 and II.

D9 page 221, Table II.

D10 page 1291, Table I.

D12 the whole document, especially page 66, figure 1.

Claims 13, 14, 16 and 18-30 are also not novel or inventive in view of D11 (see in particular page 15967, Table 1 and page 15968, Table II).

Although the above citations do not specifically disclose the dimensions defined by coordinates A, B, C and D of the present claims, presumably this framework is an inherent feature of the peptides described in D1-D12 since these compounds function as C5a antagonists or agonists.

None of D1-D12 disclose cyclic C5a antagonists or agonists corresponding to the present formulae II or IV. Consequently claims 6, 8-12, 15 and 17 are novel and inventive over the prior art.

Additional observation: Claims 19-28 and 30 are directed to methods of treatment of the human or animal body. Under Rule 67.1 of the PCT such subject matter is excluded from international preliminary examination. However, claims 19-28 and 30 have nonetheless been considered since their subject matter does not contravene Australian law.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VS:F:FP9849	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International application No. **PCT/AU 98/00490**	International filing date *(day/month/year)* 25 June 1998	Priority Date *(day/month/year)* 25 June 1997

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[6] C07K 7/06, 7/64; A61K 38/08

Applicant

1. THE UNIVERSITY OF QUEENSLAND et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **5** sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of **21** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[X]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
4 January 1999	12 October 1999
Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Marie-Anne Fam MARIE-ANNE FAM Telephone No. (02) 6283 2259

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU 98/00490

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-8, 10, 12, 17, 19-39, 44-53,** as originally filed,
pages **9, 11, 13, 15, 16, 18, 40-43,** filed with the letter of **24 August 1999.**
pages **14,** filed with the letter of **7 October 1999.**

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages **54, 56-59, 61,** filed with the letter of **24 August 1999.**
pages **55, 60, 62, 63,** filed with the letter of **7 October 1999.**

☒ the drawings, pages **1/12-12/12,** as originally filed,
pages , filed with the demand,
pages , filed with the letter of .

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , filed with the letter of .

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:
☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/fig

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos.: **1-9 (in part), 15-16 (in part), 18 (in part) and 20-32 (in part)**

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

The international search was restricted to those compounds described in the examples and defined by claims 10 and 17. Consequently the opinion on claims 1-9, 15-16, 18 and 20-32 is based only on the subject matter in so far as covered by the search.

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claim Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-32 (in part)	YES
	Claims		NO
Inventive step (IS)	Claims	1-32 (in part)	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-32	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents were identified in the international search report:

D1 Journal of Immunology, Volume 158, 1997, pages 1377-1382.
D2 Journal of Immunology, Volume 157, 1996, pages 4591-4601.
D3 Journal of Pharmacology and Experimental Therapeutics, Volume 278, 1996, pages 432-440.
D4 Immunology, Volume 86, 1995, pages 149-154.
D5 Journal of Medicinal Chemistry, Volume 34, 1991, pages 2068-2071.
D6 Journal of Immunology, Volume 153, 1994, pages 4200-4205.
D7 Journal of Medicinal Chemistry, Volume 38, 1995, pages 3669-3675.
D8 Journal of Medicinal Chemistry, Volume 40, 1997, pages 877-884.
D9 Journal of Medicinal Chemistry, Volume 35, 1992, pages 220-223.
D10 Biochemical Pharmacology, Volume 45, 1993, pages 1289-1299.
D11 Journal of Biological Chemistry, Volume 270, 1995, pages 15966-15969.
D12 Protein Science, Volume 6, 1997, pages 65-72.

None of D1-D12 disclose C5a antagonists or agonists with the dimensions defined by coordinates A, B, C and D. Consequently claims 1-32 (in part) are novel and inventive over the prior art.

Additional observation:

Claims 21-30 and 32 are directed to methods of treatment of the human or animal body. Under Rule 67.1 of the PCT such subject matter is excluded from international preliminary examination. However, claims 21-30 and 32 have nevertheless been considered since their subject matter does not contravene Australian law.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claims 1 and 15 are not fully supported by the description. The claims are exceedingly broad in scope and encompass a vast range of possible structures, however the description provides only a limited number of examples. In particular the majority of exemplified compounds are cyclic peptides of formulae II or IV; the linear derivatives described are either known from the prior art (see page 9, lines 22-37, compounds 1-7) or display reduced biological activity (see page 38, lines 9-14, compounds 8-10).

Furthermore the inventor's submissions refer repeatedly to the fact that the present invention relates to the development of cyclic agonists and antagonists, in contrast to the linear peptides of the prior art. However the claims, as presently drafted, are not limited to cyclic structures. Although claim 1 refers to a 'constrained acyclic structure', the only compound meeting this criterion and discussed in any detail appears to be the known peptide 7 (page 34, lines 13-28).

derived C5aR has been cloned and identified as a G protein-coupled receptor with transmembrane helices (Gerard and Gerard, 1991). Interactions between C5a and C5aR have been the subject of many investigations which, in summary, suggest that C5a binds via a two-site mechanism in which the N-terminal core domain of C5a is involved in receptor-recognition and binding, while the C-terminus is responsible for receptor activation. This mechanism is illustrated schematically in Figure 1. The C-terminal "effector" region alone possesses all the information necessary for signal transduction, and is thought to bind in the receptor's interhelical region (Siciliano *et al*, 1994; deMartino *et al*, 1995).

An N-terminal interhelical positively-charged region of C5a is responsible for receptor recognition and binding, and binds to a negatively-charged extracellular domain of C5aR (site 1), while the C-terminal "effector" region of C5a is thought to bind with the interhelical region of the receptor (site 2), and is responsible for receptor activation leading to signal transduction (Siciliano *et al*, 1994).

Numerous short peptide derivatives of the C-terminus of C5a have been found to be agonists of C5a (Kawai *et al*, 1991; Kawai *et al*, 1992; Kohl *et al*, 1993; Drapeau *et al*, 1993; Ember *et al*, 1992; Sanderson *et al*, 1994; Sanderson *et al*, 1995; Finch *et al*, 1997; Tempero *et al*, 1997; Konteatis *et al*, 1994; DeMartino *et al*, 1995). The structures of some of these agonists are shown in Table 2 below (compounds **1-6**). High molecular weight polypeptide inhibitors of the action of C5a at its receptor, such as monoclonal antibodies to the C5a receptor, are also known (Morgan *et al*, 1992).

A small molecule, N-methylphenylalanine-lysine-proline-D-cyclohexylalanine-tryptophan-D-arginine (**7**, MeF-K-P-dCha-W-R), is a full antagonist of the C5a receptor, with no agonist activity when tested on isolated cellular membranes (Konteatis *et al*, 1994) or intact whole cells.

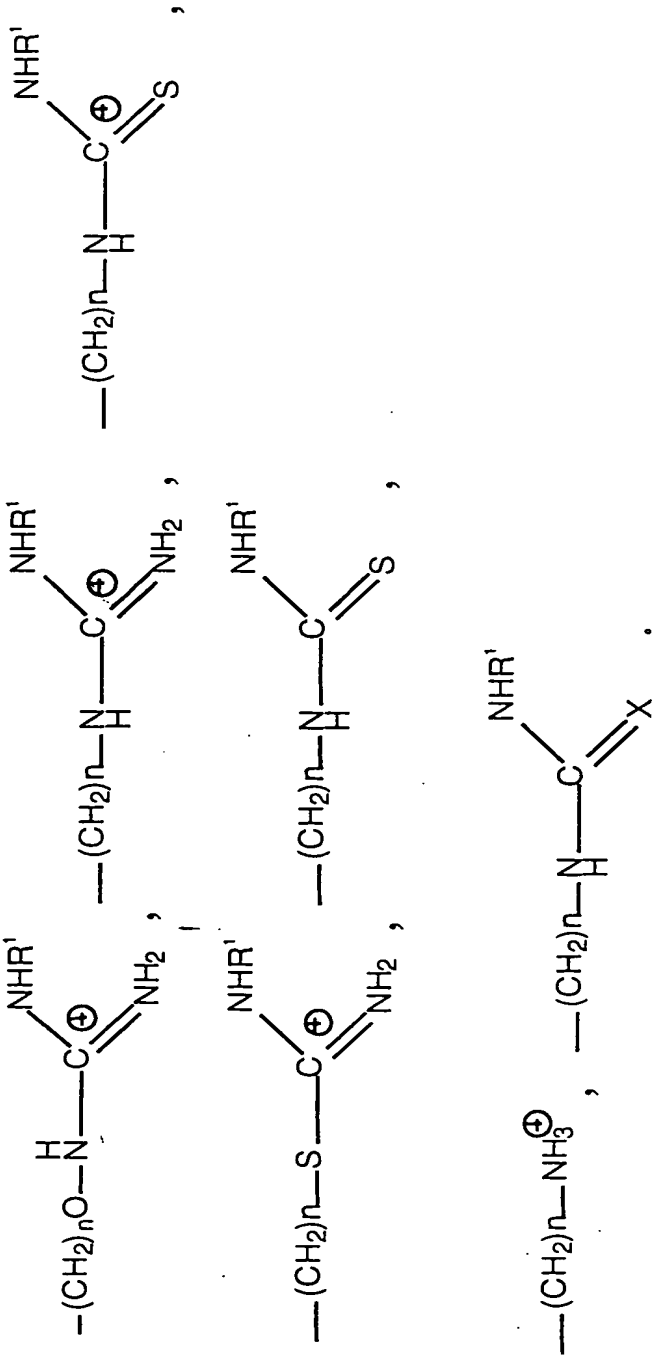
C5a antagonist or agonist binding and activity. The hexapeptide and several new structurally related antagonists have been examined for both their receptor-binding affinities and antagonist activity, using intact polymorphonuclear (PMN) cells. Our results show the hitherto unknown specific structural requirement for the binding of C5a antagonists or agonists to the C5a receptor, which we believe to be common to ligands for the G protein-coupled receptor family. Our establishment of this specific structural requirement has enabled us to design and develop improved molecular probes of the complement system and of C5a-based drugs, and to design small molecules that target other G protein-coupled receptors, which are becoming increasingly recognised as important drug targets due to their crucial roles in signal transduction (G protein-coupled Receptors, IBC Biomedical Library Series, 1996).

Thus our results have enabled us to design constrained structural templates which enable hydrophobic groups to be assembled into a hydrophobic array for interaction with a G protein-coupled receptor, for example at Site 2 of the C5a receptor illustrated in Figure 1. Such templates or scaffolds, which may be cyclic or acyclic, have not heretofore been suggested for modulators of the activity of C5a receptors or other G protein-coupled receptors.

SUMMARY OF THE INVENTION

The invention provides cyclic and non-cyclic modulators of the activity of G-protein-coupled receptors.

According to a first aspect, the invention provides a compound which is an antagonist, of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to provide a framework of approximate dimensions as follows:



where

X is NCN, NNO_2, $CHNO_2$ or NSO_2NH_2;

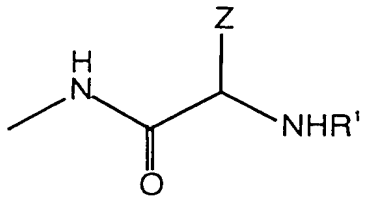
n is an integer from 1 to 4, and

R is H or an alkyl, aryl, CN, NH_2 or OH group .

B is any common or uncommon aromatic amino acid side chain which serves to position an aromatic side-chain group in this position, including but not limited to the indole, indole methyl, benzyl, phenyl, naphthyl, naphthyl methyl, cinnamyl group, or any other derivatives of these aromatic groups;

C is any common or uncommon hydrophobic amino acid side chain which serves to position any alkyl, aromatic or other group in this position, including, but not limited to D- or L-cyclohexyl alanine (Cha), leucine, valine, isoleucine, phenylalanine, tryptophan, or methionin

D is any common or uncommon aromatic amino acid which serves to position an aromatic side-chain in this position, and has the structure:



where $\bar{Z}$ includes but is not limited to indole, indole methyl, benzyl, benzene, naphthyl, naphthyl methyl, or any other derivatives of these aromatic groups, and

R^1 is H or any alkyl, aromatic, acyl or aromatic-acyl group including, but not limited to methyl, ethyl, propyl, butyl, $-CO-CH_2CH_3$, $-CO-CH_3$, $-CO-CH_2CH_2CH_3$, $-CO-CH_2Ph$, or -CO-Ph.

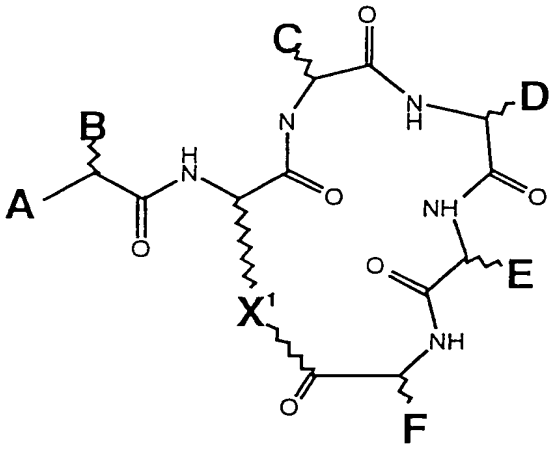
Preferably the G protein-coupled receptor is a C5a receptor.

Other cyclic or constrained acyclic molecules, which may be peptidic or non-peptide in nature, can similarly be envisaged to support groups such as A, B, C

and D for interaction with a C5a receptor or other G protein-coupled receptor.

In one preferred embodiment, the compound has antagonist activity against C5aR, has no C5a agonist activity, and has the general formula:

Structure II



where A is H, alkyl, aryl, NH_2, NHalkyl, $N(alkyl)_2$, NHaryl or NHacyl;OH, Oalkyl, Oaryl.

B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid selected from phenylalanine, homophenylalanine, tryptophan, homotryptophan, tyrosine, and homotyrosine;

C is the side chain of a D-, L- or homo-amino acid selected from the group consisting of proline, alanine, leucine, valine, isoleucine, arginine, histidine, aspartate, glutamate, glutamine, asparagine, lysine, tyrosine, phenylalanine, cyclohexylalanine, norleucine, tryptophan, cysteine and methionine;

D is the side chain of a D- or L-amino acid selected from the group consisting of cyclohexylalanine, homocyclohexylalanine, leucine, norleucine, homoleucine, homonorleucine and tryptophan;

E is the side chain of a D- or L-amino acid selected from the group consisting of tryptophan and homotryptophan;

F is the side chain of a D- or L-amino acid selected from the group consisting of arginine, homoarginine, lysine and homolysine; and

X^1 is $-(CH_2)_nNH-$ or $(CH_2)_n-S-$, where n is an integer of from 1 to 4, preferably 2 or 3, $-(CH_2)_2O-$, $-(CH_2)_3O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, or $-CH_2COCHRNH-$, where R is the side chain of any common or uncommon amino acid.

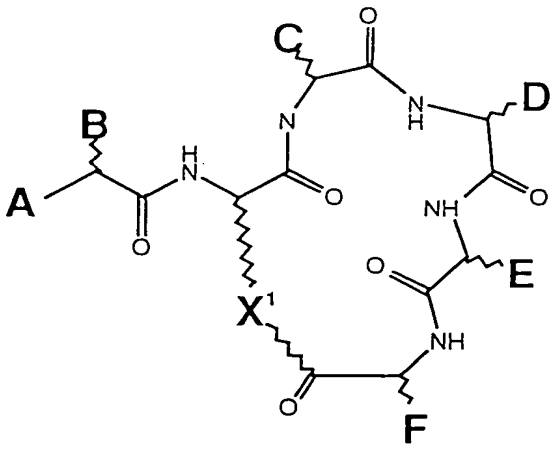
For the purposes of this specification, the term "alkyl" is to be taken to mean a straight, branched, or cyclic, substituted or unsubstituted alkyl chain of 1 to 6, preferably 1 to 4 carbons. Most preferably the alkyl group is a methyl group. The term "acyl" is to be taken to mean a substituted or unsubstituted acyl of 1 to 6, preferably 1 to 4 carbon atoms. Most preferably the acyl group is acetyl. The term "aryl" is to be understood to mean a substituted or unsubstituted homocyclic or heterocyclic aryl group, in which the ring preferably has 5 or 6 members.

A "common" amino acid is a L-amino acid selected from the group consisting of glycine, leucine, isoleucine, valine, alanine, phenylalanine, tyrosine, tryptophan, aspartate, asparagine, glutamate, glutamine, cysteine, methionine, arginine, lysine, proline, serine, threonine and histidine.

An "uncommon" amino acid includes, but is not restricted to, D-amino acids, homo-amino acids, N-alkyl amino acids, dehydroamino acids, aromatic amino acids (other than phenylalanine, tyrosine and tryptophan), ortho-, meta- or para-aminobenzoic acid, ornithine, citrulline, norleucine, γ-glutamic acid, aminobutyric acid and α,α-disubstituted amino acids.

For the purposes of this specification it will be clearly understood that the word "comprising" means

Structure IV



where E is any amino acid other than tryptophan and homotryptophan, for example D- or L- forms of alanine, leucine, valine, norleucine, phenylalanine, glutamic acid, aspartic acid, methionine, cysteine, isoleucine, serine, threonine, and F and X^1 are as defined in Structure II. Preferably the compound is an agonist of C5a.

According to a third aspect, the invention provides a composition, comprising a compound according to the invention together with a pharmaceutically-acceptable carrier or excipient.

The compositions of the invention may be formulated for oral or parenteral use, but oral formulations are preferred. It is expected that most if not all compounds of the invention will be stable in the presence of digestive enzymes. Such stability can readily be tested by routine methods known to those skilled in the art.

Suitable formulations for administration by any desired route may be prepared by standard methods, for example by reference to well-known textbooks such as Remington; The Science and Practice of Pharmacy, Vol. II, 1995 (19^{th} edition), A.R. Gennaro (ed), Mack Publishing Company, Easton, Pennsylvania, or Australian Prescription Products Guide, Vol. 1, 1995 (24^{th} edition) J. Thomas (ed),

Example 4 Cyclic Antagonists of C5a

Some examples of these cyclic antagonists and their apparent receptor-binding affinities and antagonist potencies are given in Tables 4, 5 and 6 as well as in Figures 5 and 6. In the tables the single letter code for amino acids is used.

Table 6

Effect of Cyclisation on Antagonist Binding Affinity and Antagonist Potency

	PEPTIDE	$pD_2 \pm SE^a$	IC_{50} (μM)[a]	(n)	$pD_2 \pm SE^b$	IC_{50} (μM)[b]	(n)
11	AcF-[KPdChaWR]	5.49 ± 0.22	3.2	4	7.07 ± 0.29	0.09	5
18	AcF-[OPdChaWR]	6.44 ± 0.14*	0.4	9	7.30 ± 0.09	0.05	9
19	[FWPdChaWR]	4.37 ± 0.36*	43	3	nd		
20	AcF-[KMdChaWR]	4.81 ± 0.06	15	2	nd		
21	AcF-[KKdChaWR]	3.94 ± 0.4	116	3	4.88	13	1
Effect of length of linker in cycle on antagonist binding affinity and antagonist potency							
22	AcF-[XPdChaWR]	5.02 ± 0.07	9.5	3	4.71 ± 0.23	20	3
23	AcF-[X^2PdChaWR]	4.77 ± 0.14*	17	3	6.09 ± 0.08*	0.8	4
11	AcF-[OPdChaWR]	4.60±0.06*	16	4	6.42 ± 0.10	0.4	4
24	AcKF-[OPdChaWR]	4.96 ± 0.03	11	3	6.73	0.2	1

Table 6 (cont.)

	PEPTIDE	$pD_2 \pm Se^a$	IC_{50} (μM)[a]	(n)	$pD_2 \pm SE^b$	IC_{50} (μM)[b]	(n)
14	F-[XPdChaWR]	4.39 ± 0.10*	41	3	nd		
16	F-[X^2PdChaWR]	5.42 ± 0.05	3.8	3	6.70 ± 0.04	0.4	3
25	F-[OPdChaWR]	5.51 ± 0.07	3.1	3	5.79 ± 0.34*	1.6	3
26	F-[KPdChaWR]	5.09 ± 0.08	8.1	3	5.55 ± 0.57*	2.8	3
	Effect of L-Arg on antagonist binding affinity and antagonist potency						
17	AcF-[OPdChaWR]	6.57 ± 0.05*	0.3	3	7.91 ± 0.17*	0.01	3
13	F-[XPdChaWR]	4.98 ± 0.05	10	3	5.63 ± 0.13*	2.4	3
15	F-[X^2PdChaWR]	6.50 ± 0.04*	0.3	5	7.36 ± 0.13	0.04	3
27	F-[OPdChaWR]	7.21 ± 0.01*	0.06	3	7.41 ± 0.14	0.04	3
28	F-[KPdChaWR]	6.50 ± 0.12*	0.3	4	6.69 ± 0.04	0.2	3

a pD_2/IC_{50}; concentration of peptide resulting in 50% inhibition in the binding of [^{125}I]C5a to intact PMNs. The IC50 is the antilog of the mean pD2 value

b pD_2/IC_{50}; concentration of peptide resulting in 50% inhibition in the ability of C5a (100 nM)to cause the release of MPO from PMNs

X = (CH_2)-NH_2

X^2 = $(CH_2)_2$-NH_2

pD2 values are expressed as mean ± SE

n represents the number of experiments performed

* Significant change in affinity/potency compared to NMeFKPdChaWR ($p<0.05$)

\# indicates isomer number

These results demonstrate:

(1) that the cyclic molecules have higher apparent receptor affinity and may be more potent antagonists than acyclic (linear) peptides,

(2) that one of the two possible cyclic diastereomers is consistently favoured for binding to the C5a receptor, and it is surprisingly the opposite stereochemistry (L-arginine) to that favoured in the linear compounds (D-arginine)

(3) that the cycles have an optimum ring size for receptor-binding,

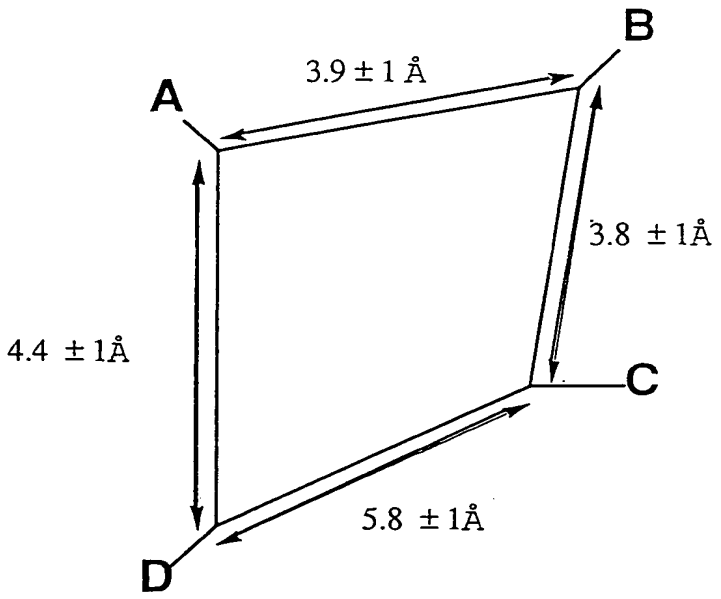
(4) that there is a pseudo-linear relationship between log (antagonist potency) and log (receptor affinity).

Tables 5 and 6 list the C5a receptor affinities of some examples of cyclic antagonists of C5a, and their ability to bind to, and inhibit, binding of C5a to human PMNs is illustrated in Figure 6. Surprisingly these data show that the L-arginine is preferred over the D-arginine, in contrast to the linear compound **7** in which the D-arginine confers higher affinity for the receptor than does L-arginine. The data also show that the size of the macrocycle is optimal when n = 2 or 3, the smaller cycle

CLAIMS:

1. A compound which is an antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic on constrained acyclic structure adapted to provide a framework of approximate dimensions as set out in Structure I:

Structure I



where the numerals refer to distances between C_α carbons of amino acids or their analogues or derivatives, and A, B, C and D are not necessarily on adjacent amino acids, or analogues or derivatives thereof; and

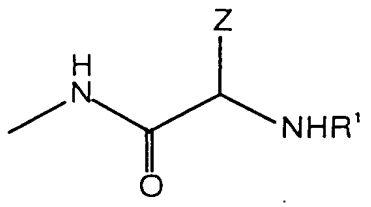
where the critical amino acid side chains are designated by A, B, C and D, where

A is any common or uncommon, basic, charged amino acid side chain which serves to position a positively charged group in this position;

B is any common or uncommon, aromatic amino acid side chain which serves to position an aromatic side-chain in this position;

C is any common or uncommon, hydrophobic amino acid side chain which serves to position any alkyl, aromatic or other group in this position;

D is any common or uncommon, aromatic amino acid which serves to position an aromatic side-chain in this position, and has the structure:



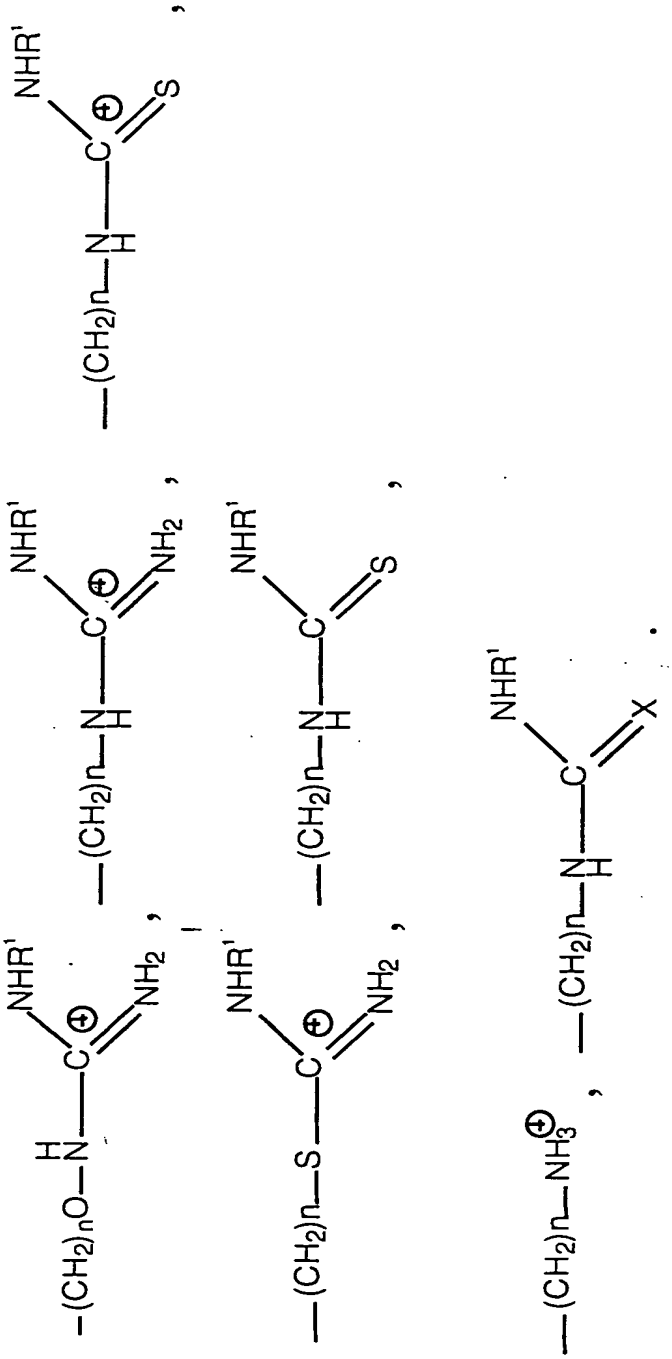
where Z is indole, indole methyl, benzyl, benzene, naphthyl, naphthyl methyl, or a derivative thereof; and

R^1 is H or an alkyl, aromatic, acyl or aromatic-acyl group.

2. An antagonist according to Claim 1, in which the G protein-coupled receptor is the C5a receptor.

3. An antagonist according to Claim 1 or Claim 2, in which

A is one of the following side-chains



or another mimetic of an arginine side chain;

where

X is NCN, NNO_2, $CHNO_2$ or NSO_2NH_2;

n is an integer from 1 to 4, and

R^1 is H or an alkyl, aryl, CN, NH_2, OH, $-CO-CH_2CH_3$, $-CO-CH_3$, $-CO-CH_2CH_2CH_3$, $-CO-CH_2Ph$, or -CO-Ph;

B is an indole, indole methyl, benzyl, phenyl, naphthyl, naphthyl methyl, cinnamyl group, or any other derivative of the aromatic group; and

C is D- or L-cyclohexylalanine (Cha), leucine, valine, isoleucine, phenylalanine, tryptophan or methionine.

4. An antagonist according to Claim 3, in which R^1 is methyl, ethyl, propyl, or butyl.

5. An antagonist according to any one of Claims 1 to 4, which is a constrained acyclic compound, and comprises a type II β-turn.

6. An antagonist according to Claim 5, in which the type II β-turn comprises a γ-turn within the type II β-turn.

7. An antagonist according to any one of claims 1 to 4, which is a cyclic peptide or peptide derivative.

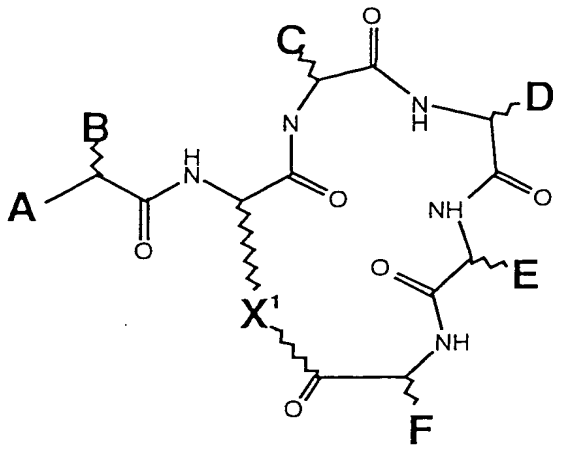
8. An antagonist according to any one of Claims 1 to 4, of formula

Ac-phe-[lys-pro-(dCha)-trp-arg] or
Ac-phe-[orn-pro-(dCha)-trp-arg]

9. An antagonist according to any one of Claims 1 to 7 in which A is L-arginine.

10. An antagonist according to Claim 1, which has antagonist activity against C5aR, has no agonist activity against C5a, and has the general formula:

Structure II



where A is H, alkyl, aryl, NH_2, NHalkyl, $N(alkyl)_2$, NHaryl or NHacyl;

B is an alkyl, aryl, phenyl, benzyl, naphthyl or indole group, or the side chain of a D- or L-amino acid selected from the group consisting of phenylalanine, homophenylalanine, tryptophan, homotryptophan, tyrosine, and homotyrosine;

C is the side chain of a D-, L- or homo-amino acid selected from the group consisting of proline, alanine, leucine, valine, isoleucine, arginine, histidine, aspartate, glutamate, glutamine, asparagine, lysine, tyrosine, phenylalanine, cyclohexylalanine, norleucine, tryptophan, cysteine and methionine;

D is the side chain of a D- or L-amino acid selected from the group consisting of cyclohexylalanine, homocyclohexylalanine, leucine, norleucine, homoleucine, homonorleucine and tryptophan;

E is the side chain of a D- or L-amino acid selected from the group consisting of tryptophan and homotryptophan;

F is the side chain of a D- or L-amino acid selected from the group consisting of arginine, homoarginine, lysine and homolysine; and

X^1 is $-(CH_2)_nNH-$ or $(CH_2)_n-S-$, $-(CH_2)_2O-$, $-(CH_2)_3O-$, $-(CH_2)_3-$, $-(CH_2)_4-$, or $-CH_2COCHRNH-$, where R is the side chain of any common or uncommon amino acid, and

where n is an integer of from 1 to 4,

11. An antagonist according to Claim 10, in which F is a L-amino acid.

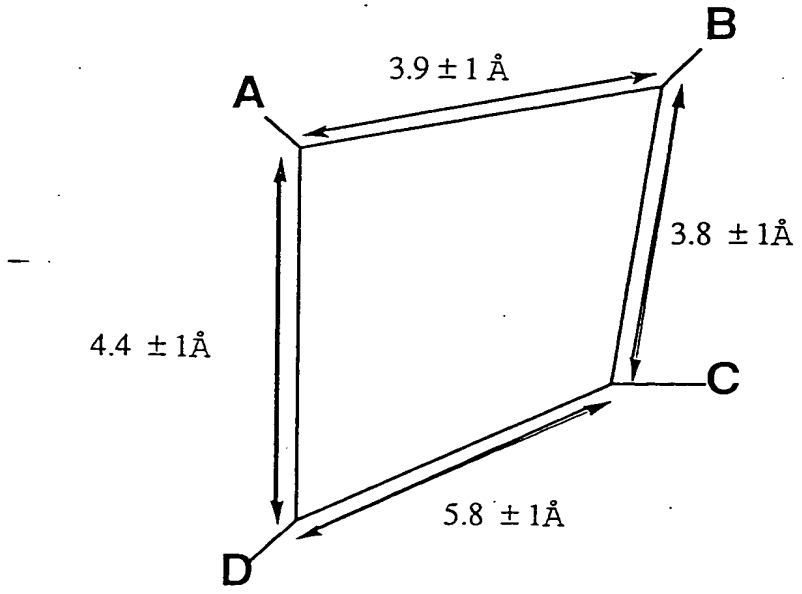
12. An antagonist according to Claim 11, in which F is L-arginine.

13. An antagonist according to any one of Claims 10 to 12, selected from the group consisting of compounds **11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27** and **28**.

14. An antagonist according to any one of Claims 3 and 10 to 13, in which n is 2 or 3.

15. A compound which is an agonist of a G protein-coupled receptor, and which has structure III

Structure III



where the numerals refer to distances between C_α carbons of amino acids or their analogues or derivatives,

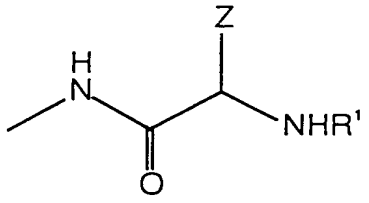
and A, B, C and D are not necessarily on adjacent amino acids, or analogues or derivatives thereof; and

where B is a non-aromatic amino acid, and

A is any common or uncommon, basic, charged amino acid side chain which serves to position a positively charged group in this position;

C is any common or uncommon, hydrophobic amino acid side chain which serves to position any alkyl, aromatic or other group in this position; and

D is any common or uncommon, aromatic amino acid which serve to position an aromatic side-chain in this position, and has the structure:



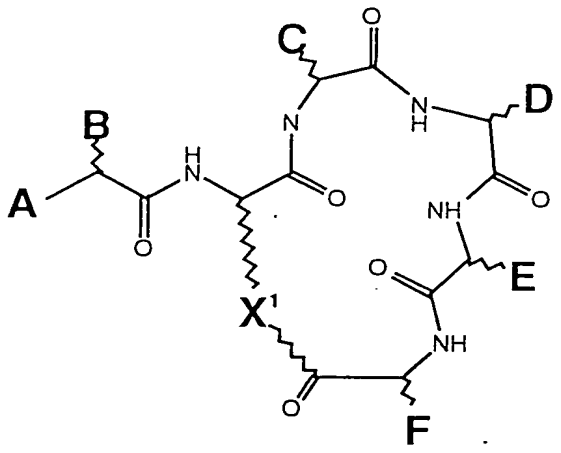
where Z is indole, indole methyl, benzyl, benzene, naphthyl, naphthyl methyl, or a derivative thereof; and

R is H or an alkyl, aromatic, acyl or aromatic-acyl group.

16. A compound according to Claim 15, where B is the D- or L-form of alanine, leucine, valine, norleucine, glutamic acid, aspartic acid, methionine, cysteine, isoleucine, serine or threonine.

17. A compound according to Claim 15 or Claim 16, in which the compound is of structure IV,

Structure IV

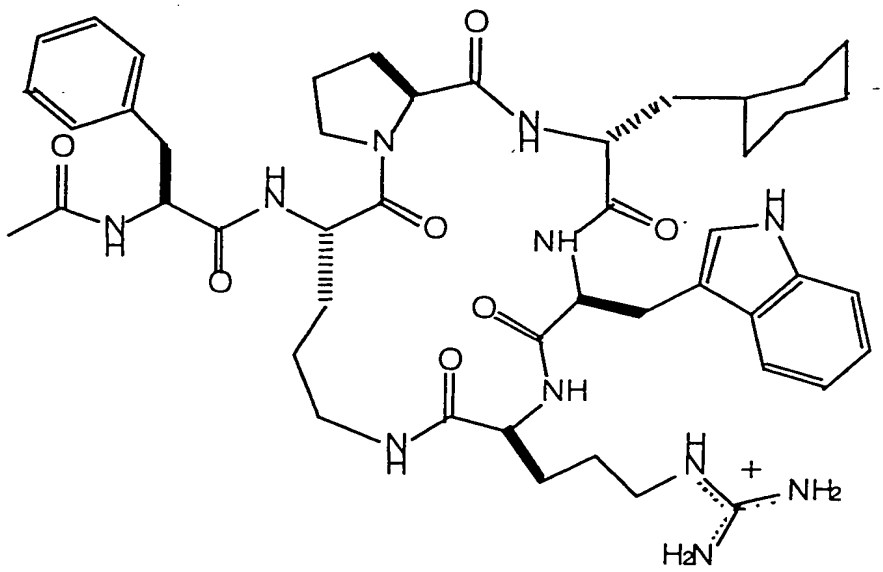


where E is any amino acid other than tryptophan and homotryptophan, and

F is the side chain of a D- or L-amino acid selected from the group consisting of arginine, homoarginine, lysine and homolysine.

18. A compound according to any one of Claims 15 to 17, wherein the compound is an agonist of C5a.

19. A compound according to Claim 10, of structure



20. A composition comprising a compound according to any one of Claims 1 to 19, together with a pharmaceutically-acceptable carrier or excipient.

21. A method of treatment of a pathological condition mediated by a G protein-coupled receptor, comprising the step of administering an effective amount of a compound according to any one of Claims 1 to 19, to a mammal in need of such treatment.

22. A method according to Claim 21, wherein the condition mediated by a G protein-coupled receptor involves overexpression or underregulation of C5a.

23. A method according to Claim 21, wherein the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischaemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome.

24. Use of a compound according to any one of Claims 1 to 19 in treatment of a pathological condition mediated by a G protein-coupled receptor.

25. Use according to Claim 24, in which the condition is mediated by C5a.

26. Use according to Claim 25, in which the condition mediated by G protein-coupled receptors involves overexpression or underregulation of C5a.

27. Use according to any one of Claims 24 to 26, in which the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischaemic heart disease, reperfusion injury, septic shock, psoriasis, gingivitis, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury and extracorporeal post-dialysis syndrome.

28. Use of a compound according to any one of Claims 1 to 19 in the manufacture of a medicament for the

treatment of a condition mediated by a G protein-coupled receptor.

29. Use according to Claim 28, in which the condition is mediated by C5a.

30. Use according to Claim 29, in which the condition mediated by G protein-coupled receptors involves overexpression or underregulation of C5a.

31. A compound according to Claim 1, substantially as hereinbefore described with reference to the examples and drawings.

32. A method according to Claim 21, substantially as hereinbefore defined with reference to the examples and drawings.